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NEWS 18	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
NEWS 19	DEC 22	ABI-INFORM now available on STN
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NEWS 21	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
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 FILE 'HOME' ENTERED AT 17:07:38 ON 01 MAR 2004

 => file medline
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 FULL ESTIMATED COST                                         0.21       0.21

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  FILE LAST UPDATED: 25 FEB 2004 (20040225/UP).  FILE COVERS 1953 TO DATE.

  On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
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  MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
  MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
  http://www.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description
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  substance identification.

 => s (ICE inhibitor) and review/dt
            9594 ICE
             157 ICES
            9651 ICE
                   (ICE OR ICES)
          228147 INHIBITOR
          471393 INHIBITORS
          575521 INHIBITOR
                   (INHIBITOR OR INHIBITORS)
             113 ICE INHIBITOR
                   (ICE(W)INHIBITOR)
          993316 REVIEW/DT
 L1            9 (ICE INHIBITOR) AND REVIEW/DT

 => d bib, abs 1-9

 L1   ANSWER 1 OF 9     MEDLINE on STN
 AN   2003348112     MEDLINE
 DN   PubMed ID: 12879740
 TI   Gamma herpesviruses: pathogenesis of infection and cell signaling.
 AU   Rajcani J; Kudelova M
 CS   Institute of Microbiology and Immunology, Jessenius Medical Faculty,
      Martin, Slovakia.. virural@savba.sk
 SO   Folia microbiologica, (2003) 48 (3) 291-318.  Ref: 188
      Journal code: 0376757. ISSN: 0015-5632.
 CY   Czech Republic
 DT   Journal; Article; (JOURNAL ARTICLE)
        General Review; (REVIEW)
      (REVIEW, TUTORIAL)
 LA   English
 FS   Priority Journals
 EM   200310
 ED   Entered STN: 20030726
      Last Updated on STN: 20031011
      Entered Medline: 20031010
 AB   Altered cell signaling is the molecular basis for cell proliferation
      occurring in association with several gamma herpesvirus infections.  Three
      gamma herpesviruses, namely EBV/HHV-4, KSHV/HHV-8 and the MHV-68 (and/or
      MHV-72) and their unusual cell-pirated gene products are discussed in this
      respect.  The EBV, KSHV as well as the MHV DNA may persist lifelong in an
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episomal form in the host carrier cells (mainly in lymphocytes but also in macrophages, in non-hornifying squamous epithelium and/or in blood vessel endothelial cells). Under conditions of extremely limited transcription, the EBV-infected cells express EBNA1 (EB nuclear antigen 1), the KSHV infected cells express LANA1 (latent nuclear antigen 1), while the MHV DNA carrier cells express the latency-associated protein M2. With the full set of latency-associated proteins expressed, EBV carrier cells synthesize additional EBNAs and at least one LMP (latent membrane protein 1). The latent KSHV carrier cells, in addition to LANA1, may express a viral cyclin, a viral Fas-DD-like **ICE inhibitor** protein (vFLIP) and a virus-specific transformation protein called kaposin (K12). In MHV latency with a wide expression of latency-associated proteins, the carrier cells express a LANA analogue (ORF73), the M3 protein, the K3/IE (immediate early) proteins and M11/bcl-2 homologue proteins. During the period of limited gene expression, the latency-associated proteins serve mainly for the maintenance of the latent episomal DNA (a typical example is EBNA1). In contrast, during latency with a broader spectrum gene expression, the virus-encoded products activate transcription of otherwise silenced cellular genes, which leads to the synthesis of enzymes capable of promoting not only viral but also cellular DNA replication. Thus, the latency-associated proteins block apoptosis and drive host cells towards division and immortalization. Proliferation of hemopoetic cells, which had become gamma herpesvirus DNA carriers, can be initiated and strongly enhanced in the presence of inflammatory cytokines and by virus-encoded analogues of interleukins, chemokines and IFN regulator proteins. At early stages of tumor formation, many proliferating hemopoetic and/or endothelium cells, which had became transcriptionally active under the influence of chemokines and cytokines, may not yet be infected. In contrast, at later stages of oncogenesis, the virus-encoded proteins, inducing false signaling and activating the proliferation pathways, bring the previously infected cells into full transformation burst.

L1 ANSWER 2 OF 9 MEDLINE on STN
AN 2003261786 MEDLINE
DN PubMed ID: 12789619
TI Pralnacasan (vertex pharmaceuticals).
AU Siegmund Britta; Zeitz Martin
CS Universitatsklinikum Benjamin Franklin, Medizinische Klinik I, Freie Universitat Berlin, Hindenburgdamm 30, 12200 Berlin, Germany.. britta.siegmund@medizin.fu-berlin.de
SO IDrugs : investigational drugs journal, (2003 Feb) 6 (2) 154-8. Ref: 46 Journal code: 100883655. ISSN: 1369-7056.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200308
ED Entered STN: 20030606
Last Updated on STN: 20030815
Entered Medline: 20030814
AB Vertex is collaborating with Aventis Pharma AG (formerly Hoechst Marion Roussel Inc) in the development of pralnacasan, an interleukin (IL)-1b converting enzyme (**ICE**) **inhibitor**, for the potential treatment of inflammatory diseases [170247], [188293], [453094].

L1 ANSWER 3 OF 9 MEDLINE on STN
AN 2002364757 MEDLINE
DN PubMed ID: 12106600
TI Interleukin-1beta converting enzyme (caspase-1) in intestinal inflammation.
AU Siegmund Britta
CS University of Colorado Health Sciences Center, Division of Infectious

Diseases B168, 4200 East Ninth Avenue, Denver, CO 80262, USA..
britta.siegmund@gmx.net
SO Biochemical pharmacology, (2002 Jul 1) 64 (1) 1-8. Ref: 82
Journal code: 0101032. ISSN: 0006-2952.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020712
Last Updated on STN: 20020808
Entered Medline: 20020807
AB An imbalance of T helper cell type 1 (Th1) versus type 2 (Th2) polarization in favor of Th1 cell subsets appears to be a key pathogenic mechanism in chronic inflammatory bowel disease (IBD), in particular in Crohn's disease. The interferon gamma-inducing factor interleukin (IL)-18 acts in strong synergism with the Th1 polarizing cytokine IL-12. Recent studies provide evidence for the participation of IL-18 in the pathogenesis of IBD: IL-18 expression is increased in inflamed lesions of Crohn's disease patients and neutralization of IL-18 in different models of experimental colitis resulted in a dramatic amelioration of disease severity. IL-18 and IL-1beta are cleaved and thereby activated by the interleukin-1beta converting enzyme (ICE). Activation of ICE also occurs during different types of infectious colitis, and ICE expression and subsequent release of IL-1beta and IL-18 significantly contribute to intestinal inflammation. ICE knockout mice as well as mice treated with the **ICE inhibitor** pralnacasan are protected against experimental mucosal inflammation. Thus, inhibition of ICE represents an intriguing new target that requires further investigation in animal models.

L1 ANSWER 4 OF 9 MEDLINE on STN
AN 2002048910 MEDLINE
DN PubMed ID: 11772244
TI ICE/Caspase-1 inhibitors as novel anti-inflammatory drugs.
AU Randle J C; Harding M W; Ku G; Schonharting M; Kurrle R
SO Expert opinion on investigational drugs, (2001 Jul) 10 (7) 1207-9. Ref: 12
Journal code: 9434197. ISSN: 1354-3784.
CY England: United Kingdom
DT Editorial
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200203
ED Entered STN: 20020125
Last Updated on STN: 20020312
Entered Medline: 20020311
AB In recent years, several strategies that selectively inhibit pro-inflammatory cytokines, have yielded effective protein-based therapies for inflammatory disorders, validating the therapeutic hypothesis that intervention in cytokine signalling can provide clinical benefit. However, these protein-based products must be administered by injection, a constraint associated with inconvenience, adverse effects and expense for patients, caregivers and insurers. Besides interfering with the effects of cytokines such as TNF-alpha or IL-1beta that have already been produced, inhibition of pro-inflammatory cytokine production or signalling with low-molecular weight orally-active drugs would combine the convenience of conventional pharmaceuticals with the focused efficacy of the protein therapies. Reducing IL-1beta and IL-18 production by inhibition of IL-1beta converting enzyme (ICE, caspase-1) is one promising

strategy because of the key roles of these cytokines in many inflammatory diseases. Pralnacasan, the first orally available, potent and selective **ICE inhibitor** to enter clinical trials, is currently under investigation in rheumatoid arthritis.

L1 ANSWER 5 OF 9 MEDLINE on STN
AN 1998029509 MEDLINE
DN PubMed ID: 9384684
TI Role of interleukin-1 beta converting enzyme (ICE) in leukemia.
AU Estrov Z; Talpaz M
CS Department of Bioimmunotherapy, University of Texas MD Anderson Cancer Center, Houston 77030, USA.
SO Cytokines and molecular therapy, (1996 Mar) 2 (1) 1-11. Ref: 130
Journal code: 9509183. ISSN: 1355-6568.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971208
AB Interleukin (IL)-1 is a proinflammatory cytokine that plays a pivotal role in driving the in vitro proliferation of leukemic cells through autocrine or paracrine pathways. Both IL-1 genes, IL-1 alpha and the prominent IL-1 beta, produce 31 kDa proteins. Whereas the precursor (pro) 31 kDa form of IL-1 alpha is biologically active, pro-IL-1 beta is inactive unless cleaved to its mature form by a cytoplasmic cysteine protease termed IL-1 beta converting enzyme (ICE). Although ICE was first thought to be a unique enzyme with a single biologic activity, several investigators have demonstrated that ICE shares sequence homology with the protein product of ced-3, the gene for cell death of the nematode Caenorhabditis elegans, and can induce apoptosis in different cellular systems. However, recent data indicate that ICE is a member of an increasingly recognized family of ICE-related molecules whose other members, such as CPP32, do not cleave pro-IL-1 beta but rather are effective inducers of apoptotic cell death. We recently investigated the effect of ICE inhibition on acute myelogenous leukemia (AML) colony growth. We found that inhibition of ICE reduced the production of mature IL-1 beta and suppressed the proliferation of AML colony-forming units, confirming the central role of IL-1 beta in AML progenitor proliferation. These data suggest that the primary role of ICE in AML cells is cleavage of pro-IL-1 beta rather than induction of apoptosis and that the antileukemic activity of specific **ICE inhibitors** warrants further exploitation.

L1 ANSWER 6 OF 9 MEDLINE on STN
AN 97340742 MEDLINE
DN PubMed ID: 9197177
TI Structure and function of interleukin-1 beta converting enzyme.
AU Tocci M J
CS Department of Molecular Immunology, Merch Research Laboratories, Rahway, New Jersey 07065, USA.
SO Vitamins and hormones, (1997) 53 27-63. Ref: 106
Journal code: 0413601. ISSN: 0083-6729.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970724

Last Updated on STN: 20000303
Entered Medline: 19970717

AB An overwhelming body of evidence has shown that IL-1 beta is a major mediator of inflammatory disease (Tocci and Schmidt, 1996). The discovery of ICE, a unique processing enzyme involved in the production of active IL-1 beta, has provided a new approach to specifically block the production of this potent cytokine. Consequently, the discovery and development of inhibitors against the enzyme could hold great promise therapeutically. Potent inhibitors of the enzyme would be useful in the treatment of a number of important inflammatory diseases and potentially in the management of leukemia (Arend, 1993b; Estrov and Talpaz, 1996). A number of key questions must be answered before the therapeutic potential of such inhibitors can be realized. The development of a pharmaceutically acceptable cysteine proteinase inhibitor will almost certainly involve new chemical strategies gauged at safely inactivating the enzyme. For such inhibitors, it will be necessary to achieve selectivity for ICE from among the growing number of ICE family members while retaining potency. It will also be important to establish the level of inhibition of IL-1 beta required to achieve therapeutic efficacy. The studies comparing IL-1 beta- and ICE-deficient mice suggest that complete abrogation of IL-1 beta is required to achieve efficacy in models of inflammation. It is not known if this is the case in humans. Understanding the source of the residual IL-1 beta produced in ICE-deficient mice will be important in order to ascertain if a similar mechanism could generate active IL-1 beta in patients receiving if a **ICE inhibitor**. As for ICE itself, a number of formidable questions remain regarding its regulation and mechanism of activation. Answering these questions experimentally will present a major challenge due to the extremely low levels of enzyme present in cells. Studies on other family members may provide easier access to some of these questions and provide clues that can be applied to ICE. The components of the pathway involved in IL-1 trafficking and secretion are unknown, as are the mechanisms of ICE activation and regulation. Clearly other cellular proteins that have yet to be discovered will be involved in each of these processes, opening up new avenues of research in this field.

L1 ANSWER 7 OF 9 MEDLINE on STN
AN 97240996 MEDLINE
DN PubMed ID: 9086432
TI Role of interleukin-1 beta converting enzyme (ICE) in acute myelogenous leukemia cell proliferation and programmed cell death.
AU Estrov Z; Talpaz M
CS Department of Bioimmunotherapy, University of Texas, M.D. Anderson Cancer Center, Houston 77030, USA.
NC CA 55164 (NCI)
SO Leukemia & lymphoma, (1997 Feb) 24 (5-6) 379-91. Ref: 113
Journal code: 9007422. ISSN: 1042-8194.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970721
Last Updated on STN: 20000303
Entered Medline: 19970708

AB The proinflammatory cytokine interleukin (IL)-1 has been shown to play a pivotal role in stimulating acute myelogenous leukemia (AML) cell proliferation. The gene for its prominent IL-1 beta form produces a 31-kDa precursor protein (pro-IL-1 beta) that is biologically inactive unless cleaved to its mature form by a cytoplasmic cysteine protease termed Il- 1 beta converting enzyme (ICE). Although ICE was first thought to be a unique enzyme with a single biologic activity, several

investigators have demonstrated that ICE shares sequence homology with the protein product of ced-3, the gene for cell death of the nematode Caenorhabditis elegans, and induces apoptosis in different experimental models. It was therefore hypothesized that ICE may either augment the production of mature IL-1 beta and stimulate the proliferation of cells, in which IL-1 beta acts as an autocrine growth factor, or induce apoptosis. Recent data indicate that ICE is a member of an increasingly recognized family of cysteine proteases. Unlike ICE, the other members of this family do not cleave pro-IL-1 beta but are effective inducers of apoptotic cell death, whereas ICE acts primarily as an IL-1 beta converting enzyme. Because IL-1 beta serves as either an autocrine or paracrine growth factor in AML, we recently investigated the effect of ICE inhibition on AML colony growth and found that ICE inhibition reduced the production of mature IL-1 beta and suppressed AML progenitor proliferation. Our data suggest that ICE does not function as an apoptosis gene in AML but rather increases mature Il-1 beta production and AML cell proliferation. It is possible, therefore, that **ICE inhibitors** may be beneficial in AML therapy.

L1 ANSWER 8 OF 9 MEDLINE on STN
AN 97168133 MEDLINE
DN PubMed ID: 9015750
TI In vitro and in vivo studies of **ICE inhibitors**.
AU Livingston D J
CS Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts 02139, USA.
SO Journal of cellular biochemistry, (1997 Jan) 64 (1) 19-26. Ref: 52
Journal code: 8205768. ISSN: 0730-2312.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970523
Last Updated on STN: 20000303
Entered Medline: 19970512
AB Interleukin-1 beta-converting enzyme (ICE) is a cysteine protease responsible for proteolytic activation of the biologically inactive interleukin-1 beta precursor to the proinflammatory cytokine. ICE and homologous proteases also appear to mediate intracellular protein degradation during programmed cell death. Inhibition of ICE is a new antiinflammatory strategy being explored by the design of both reversible inhibitors and irreversible inactivators of the enzyme. Such compounds are capable of blocking release of interleukin-1 beta from human monocytes. **ICE inhibitors** that cross react against multiple ICE homologs can also block apoptosis in diverse cell types. **ICE inhibitors** impart protection in vivo from endotoxin-induced sepsis and collagen-induced polyarthritis in rodent models. Further optimization of the current generation of peptidyl **ICE inhibitors** will be required to produce agents suitable for administration in chronic inflammatory and neurodegenerative diseases.

L1 ANSWER 9 OF 9 MEDLINE on STN
AN 97070864 MEDLINE
DN PubMed ID: 8913790
TI Microbial/host interactions in health and disease: who controls the cytokine network?.
AU Henderson B; Poole S; Wilson M
CS Maxillofacial Surgery Research Unit Eastman Dental Institute for Oral Health Care Sciences, University College London, UK..
b.henderson@eastman.ucl.ac.uk
SO Immunopharmacology, (1996 Oct) 35 (1) 1-21. Ref: 126

Journal code: 7902474. ISSN: 0162-3109.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199703
ED Entered STN: 19970313
Last Updated on STN: 19970313
Entered Medline: 19970304
AB The interacting cellular and molecular systems which we classify as immunity and inflammation evolved to protect the organism from exogenous parasites including viruses and bacteria. Cytokines play a pivotal, but paradoxical, role both in immunity and inflammation. These local peptide hormone-like molecules form a major arm of the organisms, defenses against infectious microorganisms but they are also implicated as potent mediators of the pathology of infectious diseases. The apparently lethal effects of interleukin-1 and tumor necrosis factor in experimental septic shock testify to the latter. In the current paradigm, cytokine induction, as a protective or pathological mechanism, is a direct response to the presence of infectious microorganisms. Evidence is now accumulating that cytokines play a much more complex role in the interplay between exogenous microorganisms and the host. For example, it has been established that viruses have evolved pro-active methods of subverting the cytokine network by producing: (i) soluble cytokine receptors which bind and inactivate cytokines, (ii) immunomodulatory cytokine homologues, and (iii) **ICE inhibitors**. The possibility exists that the major role of these 'viral cytokines' is to neutralize certain host responses. Recent cytokine transgenic knockouts demonstrate that the normal benign response to commensal gut microflora becomes a lethal inflammatory state in the absence of the cytokines interleukin 2 or interleukin 10. The human body contains an enormous number of microorganisms which constitute the normal microflora. It is estimated that the average human contains 10(13) eukaryotic cells but 10(14) bacteria. We propose that the ability of the multicellular organism to live harmoniously with its commensal microflora must depend on mutual signalling involving eukaryotic cytokines and prokaryotic cytokine-like molecules. Such interactive signalling sets up non-inflammatory cytokine networks in tissues which form the background on which responses to infectious microorganisms must be built and related. The capacity of bacteria to induce cytokine synthesis was believed to be due to a small number of components, such as lipopolysaccharide (LPS), which is only active as a complex with host factors (lipopolysaccharide binding protein and CD14). However, it is now clear that bacteria contain and produce a large number of diverse molecules which can selectively induce the synthesis of both pro-inflammatory and immunomodulatory/anti-inflammatory cytokines. Many toxins are potent inducers of cytokine release or synthesis and some can inhibit LPS-induced cell activation. We have introduced the term bacteriokine to describe these bacterial cytokine inducers. The question that has to be addressed therefore is - who controls the cytokine network (eukaryotic or prokaryotic cells) and how is it controlled? It is proposed that an understanding of this question will bring with it an understanding of how to control the pathological inflammatory response and may allow the development of truly effective anti-inflammatory agents.